REMARKS

Response to Restriction Requirement

The Examiner has restricted the prosecution of the present application to either Group I (claims 1-6, 9-10 and 15) or Group II (claims 7-8, 11-14 or 16-20). Applicants confirm the election of the claims of Group I, without traverse.

The claims of Group I are directed to assays to determine whether a compound enhances the clearance of a cholesterol-containing lipoprotein by assessing whether the test compound binds to the lipoprotein in manner that changes the three-dimensional conformation of the lipoprotein and increases its binding to a lipoprotein receptor.

Rejection of Claims under 35 U.S.C. § 112

Original claims 1-6, 9, 10 and 15 were rejected under 35 U.S.C. § 112, second paragraph for failing to particularly point out and distinctly claim the subject matter that Applicants regard as their invention. In response to the Examiner's concerns, Applicants have amended these claims for clarification.

Prior Art Rejections

As discussed above, the amended claims are directed to a method to determine whether a compound will increase the clearance of a low density lipoprotein in a host, that includes mixing the compound with low density lipoprotein; determining whether the compound and the low density lipoprotein form a complex; and determining whether the complex alters the three dimensional conformation of the lipoprotein such that the binding of the lipoprotein to a lipoprotein receptor is enhanced. As stated on pages 13-14 of the application, prior to this discovery, it was not known that one could lower serum cholesterol by administering a compound that intercalates into cholesterol-bearing LDL in a manner that increases binding

efficiency to clearing receptors. Since the present claims are assay claims based on this novel mechanism of action, they can not be rendered obvious by the prior use or disclosure of compounds to lower cholesterol that either act through unrelated mechanisms or which act through unknown mechanisms, neither of which would teach the public to carry out the present assay.

Rejection of Original Claims 1-3, 6 and 15 Under 35 U.S.C. § 102 (b) as Anticipated by Mao *et al.* (WO95/15760)

Mao *et al.* discloses administering certain 2,6-di-alkyl-4-silyl-phenols including those synthesized on pages 7-14 to lower cholesterol levels in patients with hypercholesterolemia. Mao does not address the mechanism of action of these compounds, and therefore, could not disclose or render obvious a screen based on discovery of a mechanism of action. Mao does not, in fact, disclose any screening procedures, because the Mao invention is based on a identification of a class of compounds to lower cholesterol through an unknown or undescribed pathway.

In order for an inherency rejection under 35 U.S.C. § 102 (b) to be maintained, the Examiner must provide factual and technical grounds establishing that the inherent features of the current invention necessarily flows form the teachings of the prior art. Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Int. 1990); see also In re Oerlich, 666 F.2d 578, 581, 212 USPQ 3232, 326 (CCPA 1981) (Inherency must flow as a necessary conclusion form the prior art, sot simply a possible one). Thus, the Examiner must make in initial *prima facie* case of inherency before the burden shifts to the Applicants to demonstrate that the prior art does not inherently possess the recited features of the claimed invention. See In re King, 801 F.2d 1324, 1327, 231 USPQ 430, 432-433 (CCPA 1977). Applicants submit that in the instant case, the Examiner has not established a *prima facie* case for inherency.

The current application is directed to *methods of assessing* the ability of a compound to enhance LDL clearance. The methods disclosed in the current application can be used to assess LDL clearance either *in vivo* or *in vitro*. In contrast, Mao *et al.* disclose a *method of lowering cholesterol* in a patient. Based on the teaching of Mao, one of ordinary skill in the art would not be taught to carry out the presently claimed screening methods.

Applicants also point out that no claim amendments were made to overcome this rejection.

Rejection of Original Claims 1-3, 6 and 15 Under 35 U.S.C. § 102(b) as Anticipated by Grundy (New England Journal of Medicine 319:24-33, 1988)

Applicants first wish to point out that the Office Action mailed February 2, 2001 inadvertently identifies the 1988 New England Journal of Medicine as being authored by Oates *et al.* Applicants respectively wish to point out that the correct author is Grundy. The Examiner suggests that original claims 1-3, 6 and 15 are anticipated under 35 U.S.C. § 102(b) by Grundy. Grundy teaches a compound or drug (mevastatin or compactin and lovastatin) that inhibits HMG-CoA reductase and markedly lowers cholesterol and LDL levels in patients.

Grundy on its face teaches that the disclosed compounds act through a different mechanism than that which is the basis of the claimed screen. In particular, Grundy teaches that the compounds are 3-hydroxy-3-methylglutaryl coenzyme A (i.e., HMG-A) reductase inhibitors. The present screen selects for compounds which effectively intercalate into cholesterol-bearing lipoprotein. These two mechanism are completely unrelated. No person of ordinary skill would

be taught to carry out the present screen, or even be motivated to try the present screen, by the disclosure of HMG-A reductase inhibitor compounds to lower cholesterol.

Applicants also point out that no claim amendments were made to overcome this rejection.

Rejection of Original Claims 1-5 and 9-10 Under 35 U.S.C. § 102(e) as Anticipated by U.S. Patent No. 6,107,045 to Koren *et al*

The Examiner has rejected original claims 1-5 and 9 and 10 under 35 U.S.C. § 102(e) as being anticipated by Koren *et al*. Koren discloses compositions and methods using antibodies that are immunoreactive with specific apolipoproteins to determine the concentration of lipoproteins such as HDL and LDL and or apolipoproteins in human blood, serum or plasma. Monoclonal antibodies are described by Koren that specifically bind to epitopes present on the apolipoprotein. Koren *et al* don't address how to lower serum cholesterol, nor do they describe any test compound screens for small molecule therapeutics. The Koren patent provides no information on the issue of modulating the conformation of a lipoprotein for therapeutic purposes.

Applicants also point out that no claim amendments were made to overcome this rejection.

CONCLUSION

Based on the above-presented amendments and comments, Applicants request that the Examiner allow all pending claims.

Respectfully submitted,

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Marked-Up Version of Original Claims

Claims 1, 2, 4-6, 9, 10 and 15 have been amended as follows:

1. (Amended) A method to assess whether a compound **enhances the clearing of a** ~~is an LDL clearance enhancing drug that includes mixing the drug with~~ cholesterol-containing **low-density** lipoprotein **in a host human or animal comprising** ~~*in vivo* or *in vitro*; isolating the complex, and determining whether the binding of the compound to the complex causes a change in the three dimensional conformation of apoB-100 in the lipoprotein that enhances the binding affinity of the lipoprotein to the LDL receptor; wherein the LDL-clearance enhancing drug is not probucol or a mono- or di-ester of probucol, not a compound described in WO 98/09773, and not a silyl compound described in U.S. Patent Nos. 5,155,250 or 5,608,095.~~

(a) administering the compound to the host ;

(b) isolating cholesterol-containing low density lipoprotein from the host,

(c) determining whether the compound has bound to the cholesterol-containing lipoprotein to form a complex; and

(d) determining whether the complex causes a change in the three dimensional conformation of the lipoprotein that enhances the binding affinity of the lipoprotein to the LDL receptor.

2. (Amended) The method of claim 1, wherein the ~~cholesterol-containing lipoprotein is LDL~~ **compound changes the conformation of apolipoprotein in the low density lipoprotein (LDL)**.

4. (Amended) The method of claim 1, wherein the binding of the compound to the complex is ~~determined~~ **assessed** by a sandwich ELISA.

5. (Amended) The method of claim 1, wherein the binding of the compound to the complex is ~~determined~~ **assessed** using agarose electrophoresis.

6. (Amended) A method ~~to alter the conformation of a cholesterol-containing lipoprotein comprising mixing the cholesterol-containing lipoprotein *in vivo* or *in vitro* with a compound and~~

~~determining whether the binding of the compound to the complex causes a change in the three dimensional conformation of apoB-100 in the lipoprotein that enhances the binding affinity of the lipoprotein to an LDL receptor~~ **determine whether a compound will increase the clearance of a low density lipoprotein in a host, comprising**

(i) mixing the compound with low density lipoprotein;

(ii) determining whether the compound and the low density lipoprotein form a complex; and

(iii) determining whether the complex alters the three dimensional conformation of the lipoprotein such that the binding of the lipoprotein to a lipoprotein receptor is enhanced.

9. (Amended) A method to determine ~~whether a high plasma cholesterol level in a host is due to a genetic alteration of the host's apoB-100 protein comprising administering a LDL clearance enhancing drug to the patient, observing a lower than normal decrease in plasma cholesterol level, and then isolating and evaluating the host's apoB-100 protein~~ **to determine if a compound causes a change in the structure of apolipoprotein B-100 in a cholesterol-containing low density lipoprotein that would be therapeutically useful, comprising:**

(i) mixing the compound with low density lipoprotein;

(ii) carrying out a sandwich immunoreactivity assay on the compound low density lipoprotein mixture using an antibody directed to the epitope on apolipoprotein B-100 that binds to the LDL-receptor,

(iii) using a second antibody to quantify the amount of LDL captured by the assay; and

(iv) comparing the amount of LDL captured by the assay to a control.

10. (Amended) ~~A~~ **The** method ~~to determine whether a high plasma cholesterol level in a host is due to a genetic alteration of the host's apoB-100 protein comprising exposing the host's apoB-100 protein to an LDL clearance enhancing drug in vitro under conditions in which the host's apoB-100 protein and the drug can form a complex, and then isolating and evaluating the change in conformation of the host's apoB-100 protein caused by any complexation~~ **of claim 6, wherein the conformational change in lipoprotein is assessed by observing a change in the electrophorectic mobility pattern of the lipoprotein using electrophoresis**.

15. (Amended) A method for assessing whether a compound ~~binds to a lipoprotein in a manner which lowers plasma cholesterol comprising complexing the compound with cholesterol-containing lipoprotein, isolating the resulting complex, and determining whether the binding of the compound to the complex causes a change in the three dimensional conformation of apoB-100 in the lipoprotein that enhances the binding affinity of the lipoprotein to the LDL receptor~~ **enhances the binding of the lipoprotein to a lipoprotein receptor and thus lowers plasma cholesterol, the method comprising:**

(a) allowing the compound to form a complex with a cholesterol-containing lipoprotein in vivo,

(b) isolating the resulting complex, and

(c) determining whether the formation of the complex causes a change in the three dimensional conformation of apoB-100 in the lipoprotein that enhances the binding of the lipoprotein to the LDL hepatic receptor.